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(54) Title: CCR–3 RECEPTOR ANTAGONISTS

(57) Abstract

CCR–3 receptor antagonists and novel methods for their use are provided.

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CCR-3 RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to the use of ketone and amide derivatives, and pharmaceutical compositions containing these compounds as Chemokine/CCR-3 receptor antagonists.

Chemokines are a superfamily of small secreted proteins. There are approximately 30 distinct chemokines known with many others being characterized. See Oppenheim et al., Properties of the Novel Proinflammatory Supergene "Intercrine" Cytokine Family, Ann. Rev. Immun. , 9, 617-648 (1991); and Baggiolini, et al., Interleukin-8 and Related Chemotactic Cytokines-CXC and CC Chemokines, Adv. Immun., 55, 97-179 (1994). The properties of the chemokines suggest that they are essential for leukocyte trafficking and inflammatory processes, and are thus important components in a number of disease states. See Kita et al., Chemokines Active on Eosinophils: Potential Roles in Allergic Inflammation, J. Exp. Med., 183, 2421-2426 (1996); Strieter, et al., "The Good, the Bad and the Ugly" The Role of Chemokines in Models of Human Diseases, J. Immun., 157, 3583-3586 (1996); and Baggiolini, Eotaxin: a VIC (Very Important Chemokine) of Allergic Inflammation, J. Clin. Invest., 97, 587 (1996).

Chemokines mediate their effects via interactions with 7TM-G-protein coupled receptors on the surface of immune and inflammatory cells. Eosinophils are proinflammatory granulocytes that play a major role in allergic diseases, such as bronchial asthma, allergic rhinitis, pruritis and atopic dermatitis. Upon activation, eosinophils release lipid mediators, cytotoxic proteins, oxygen metabolites and cytokines, all of which have the potential to produce pathophysiology. Numerous studies have demonstrated the presence of eosinophils or eosinophil-specific products in inflamed tissues in human diseases.

The mechanisms responsible for the selective infiltration of eosinophils in allergic diseases have yet to be clarified. Recently, a CC chemokine, Eotaxin, was identified in guinea pigs and demonstrated to be present in a guinea pig model of allergic airway inflammation. See Jose, et al., Eotaxin: A Potent Eosinophil Chemoattractant Cytokine Detected in Guinea Pig Model of Allergic Airways

Inflammation, J. Exp. Med., 179, 881-887 (1994); and Jose, et al., Eotaxin: Cloning of an Eosinophil Chemoattractant Cytokine and Increased mRNA Expression in Allergen-challenged Guinea-pig Lungs, Biochem. Biophys. Res. Comm., 205, 788-794 (1994). The human homologue of Guinea-pig eotaxin has been expressed and has been shown to induce eosinophil infiltration when injected into the skin of the rhesus monkey. See Ponath, et al., Cloning of the Human Eosinophil Chemoattractant, Eotaxin: Expression, Receptor Binding, and Functional Properties Suggest a Mechanism for Selective Recruitment of Eosinophils, J. Clin. Invest., 97, 604-612 (1996).

The cloning, expression and characterization of a novel C-C chemokine receptor, designated CCR-3 from peripheral blood eosinophils and from an eosinophil cDNA library have also been reported. See Kitaura, et al., Molecular Cloning of Human Eotaxin, an Eosinophil-selective CC Chemokine, and Identification of a Specific Eosinophil Eotaxin Receptor, CC Chemokine Receptor 3, J. Biol. Chem., 271, 7725-7730 (1996); Ahuja, et al., Cloning and Functional Expression of a Human Eosinophil CC Chemokine Receptor, J. Biol. Chem., 270, 16491-16494 (1995); Daugherty, et al., Cloning, Expression and Characterization of the Human Eosinophil Eotaxin Receptor, J. Exp. Med. 183, 2349-2354 (1996); and Ponath, et al., Molecular Cloning and Characterization of a Human Eotaxin Receptor Expressed Selectively on Eosinophils, J. Exp. Med., 183, 2437-2448 (1996).

Eotaxin, MCP-4 and, to a lesser extent, RANTES and MCP-3 activate this receptor. The CCR-3 receptor is expressed at high levels on eosinophils; typically 40,000- 400,000 receptors per cell are present. This is 10-100 fold more than the other chemokine receptor (CCR-1) expressed in eosinophils. Monoclonal antibodies raised to the CCR-3 receptor demonstrate that the receptor is primarily restricted to eosinophils and a subset of Th2 T-cells. This restricted expression on eosinophils and T-cells may be responsible for the selective recruitment of eosinophils and Th2 T-cells in allergic inflammation. Additionally, CCR-3 is potently activated by eotaxin 1, eotaxin and MCP-4. See Stellato et al., Production of the Novel CC Chemokine MCP-4 by Airway Cells and Comparison of Its Biological Activity to other CC-Chemokines. J. Clin. Invest. 99 926-936 (1997). In contrast, other known

chemokines appear to activate more than one chemokine receptor. e.g. RANTES binds to CCR-1, CCR-3, CCR-4 and CCR-5 receptors.

The foregoing research advances have provided the impetus to investigate the inhibition of eosinophil-specific chemokines in order to examine its role in blocking cellular infiltration in inflamed tissues. CCR-3 receptor antagonists thus offer a unique approach toward decreasing the pathophysiology associated with allergic diseases. Antagonism of this receptor may be useful in the treatment of allergic disorders, including but not limited to bronchial asthma, allergic rhinitis, eczema, nasal polyposis, conjunctivitis, atopic dermatitis, inflammatory bowel disorder and pruritis.

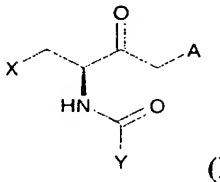
SUMMARY OF THE INVENTION

The present invention involves ketone derivatives represented by Formulas (I) and (II) hereinbelow and their use as CCR-3 receptor antagonists which is useful in the treatment of a variety of diseases associated with allergic disorders, including but not limited to bronchial asthma, eczema, allergic rhinitis, conjunctivitis, nasal polyposis, atopic dermatitis, pruritis and inflammatory bowel disease.

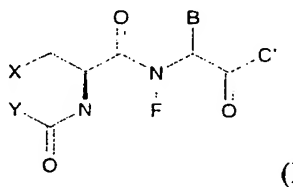
The present invention further provides methods for antagonizing CCR-3 receptors in an animal, including humans, which comprises administering to a subject in need of treatment an effective amount of a compound of Formula (I) or (II) as indicated hereinbelow.

DETAILED DESCRIPTION OF THE INVENTION

The compounds useful in the present methods are selected from Formulas (I) and (II) hereinbelow:



(I)



(II)

wherein:

A represents OR_1, NR_1 or SO_nR_1;

n = 0,1 or 2;

R_1 and R_2 are, independently, selected from the group consisting of hydrogen, C_{1-6}alkyl, alkylaryl, arylalkyl and aryl;

X represents optionally substituted aryl or heteroaryl;

Y represents optionally substituted aryl or heteroaryl;

C' represents NR_1R_2;

B represents hydrogen, methyl, aryl, alkylaryl or arylalkyl; and

F represents hydrogen, C_{1-6}alkyl or aryl.

Preferably, A is selected from the group consisting of O-phenyl, NH-phenyl, S-phenyl and SO_2-phenyl.

Preferably, C' is selected from the group consisting of NH-phenyl, N(CH_3)-phenyl and NH-(3-pyridinyl).

Preferably, F is selected from hydrogen or CH_3.

As used herein, "alkyl" refers to an optionally substituted hydrocarbon group joined together by single carbon-carbon bonds. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or unsaturated. Preferably, the group is linear. Preferably, the group is unsubstituted. Preferably, the group is saturated. Preferred alkyl moieties are C_{1-4} alkyl, most preferably methyl.

As used herein, "aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. "Aryl" includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. Preferred aryl moieties are phenyl or naphthyl, unsubstituted, monosubstituted, disubstituted or trisubstituted. Preferred heteroaryl moieties are selected from the group consisting of unsubstituted, monosubstituted, disubstituted or trisubstituted thienyl, quinolinyl, indolyl and pyridinyl. Preferred aryl and heteroaryl substituents are selected from the group consisting of C_{1-4} alkyl, NC_{1-4} alkyl, halo, OC_{1-4} alkyl, CH=CH, CF_3, pyridine, phenyl, NO_2, OH and MeO.

More preferably, alkyl substituents are methyl or ethyl. More preferably, halo substituents are chloro or bromo.

Preferred compounds of formula (I) useful in the present invention are selected from the group consisting of:

1-Phenoxy-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone;

1-Mercaptophenyl-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone;

1-Sulfonylphenyl-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone; and

1-Phenylamino-3-(S)-(N-(1-naphthoyl)amino)-4-(4-chlorophenyl)-2-butanone.

Preferred compounds of formula (II) useful in the present invention are selected from the group consisting of:

(S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)propionylamino]-(*N*-phenyl)acetamide;

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-chlorophenyl)propionylamino]-(*N*-phenyl)propionamide;

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)propionylamino]-(*N*-methyl-*N*-phenyl)propionamide;

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-chlorophenyl)propionylamino]-*N*-(3-pyridyl)propionamide;

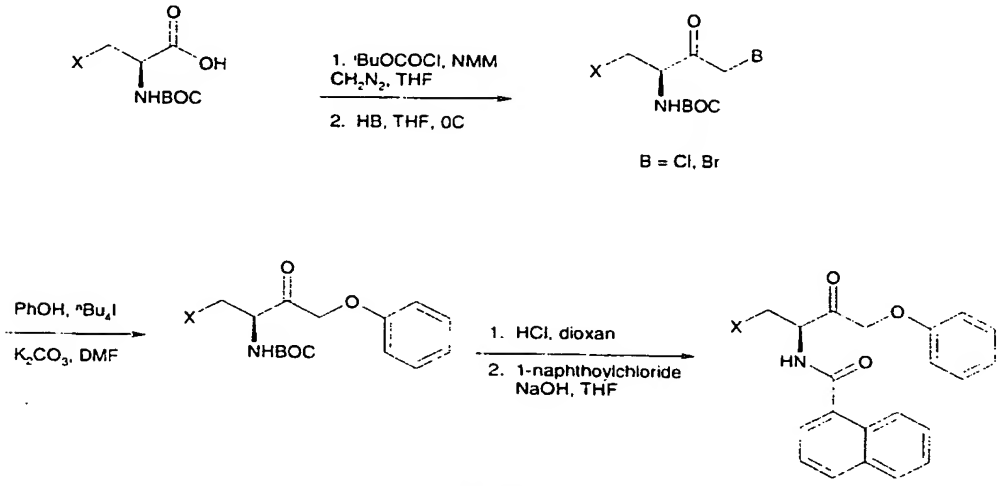
(S),(S)-2-[2-(1-naphthoylamino)-3-(4-chlorophenyl)-*N*-methylpropionylamino]-(*N*-phenyl)propionamide; and

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)-*N*-methylpropionylamino]-(*N*-phenyl)propionamide.

A particularly preferred compound is (S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)propionylamino]-(*N*-phenyl)acetamide.

Also included in the present invention are pharmaceutically acceptable salt complexes. Preferred are the ethylene diamine, sodium, potassium, calcium ethanolamine, hydrochloride, hydrobromide and trifluoroacetate salts. The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

Compounds of the present claim of formula (I) are readily prepared by conventional alkylation methods well known to those skilled in the art and are exemplified by Scheme 1 below:

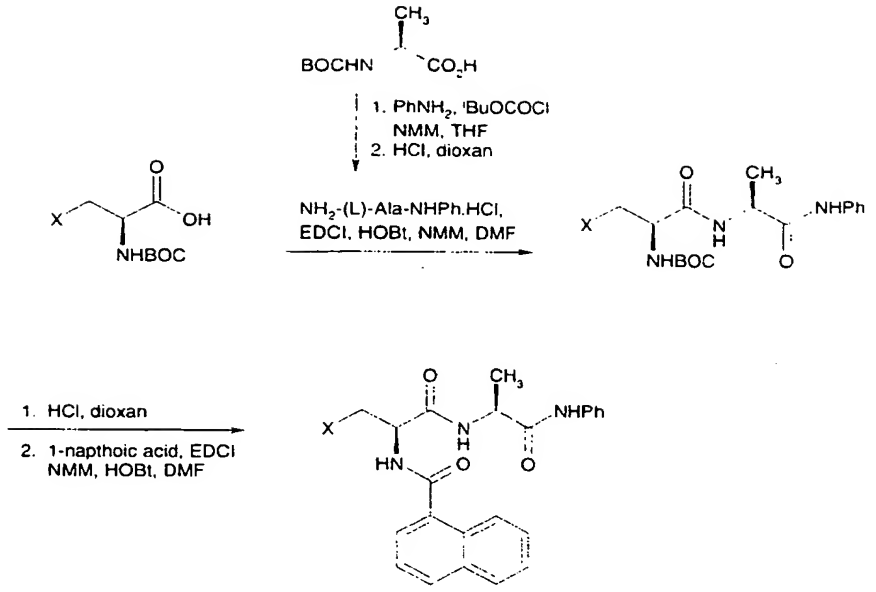


Scheme 1

With appropriate manipulation and protection of any chemical functionality, synthesis of the remaining compounds of Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of the present claim of formula (II) are readily prepared by conventional acylation methods (for example as used in peptide synthesis) well known to those skilled in the art and are exemplified by Scheme 1A below:



Scheme 1A

With appropriate manipulation and protection of any chemical functionality, synthesis of the remaining compounds of Formula (II) is accomplished by methods analogous to those above and to those described in the Experimental section.

As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease.

The present compounds are useful for the treatment of diseases including but not limited to bronchial asthma, eczema, allergic rhinitis, conjunctivitis, nasal polyposis, atopic dermatitis, pruritis and inflammatory bowel disease.

Compounds of Formula (I) and (II) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, dermally, transdermally, rectally, via inhalation or via buccal administration.

Composition of Formula (I) and (II) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules, creams and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil. olive oil, glycerine or water

with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) and/or (II) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg/Kg, of a compound of Formula(I) or (II) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I) or (II).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula(I) or (II) or a pharmaceutically acceptable salt thereof calculated as the free acid. the daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof calculated as the free acid. the daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) or (II) are demonstrated by the following test:

Human eosinophils were purified by standard CD16 cell depletion using a Miltenyi cell separation column and a magnetic Super Macs magnet. Eosinophils which were >95% pure as assessed by DiffQuick staining and light microscopy were washed in PBS and resuspended in binding buffer (RPMI-1640 + 25mM Hepes + 0.1% Gelatin + 0.1% sodium azide + 0.008% CHAPS). Into a 96 well plate (Dynatek) 200,000 eosinophils, 0.25 nM 125I-Eotaxin (Amersham Plc), and compound of interest (1 nM to 100 uM) was added. This mixture of cells compound and ligand was allowed to incubate for 60 min at room temperature before harvesting. For harvesting, free ligand from bound ligand was separated over a

Packard Unifilter-96 GFC, (cat #6005174) which had been pre-blocked with 1% polyethylenimine (Sigma Cat # P3143) and 1% Bovine Serum Albumin (BSA) for 2 hours prior to use. After drying, and sealing the plate with Topseal (Packard Topseal A Cat # 6005185) 50 ul of MicroScint (Packard Microscint-20 Cat # 6013621) was added to each well. Bound from free 125I-eotaxin was separated using a Packard Filtermate 196, 96-well plate harvester. To determine total and non-specific binding (NSB) three wells for each condition were set aside. For total binding and NSB, wells received all additions except compound. In addition NSB wells received 200 nM cold eotaxin (PeproTech, Rocky Hill, NJ). Radioactivity associated with the filter was assessed in a Packard Top-count Microplate Scintillation Counter model number 49872V. Percent control binding was assessed by first subtracting the NSB from each well and then expressing the number of counts (CPM) associated with the compound treated sample as a percent of the control binding in the absence of compound addition.

Animal model for the *in vivo* evaluation of CCR-3 antagonists

Guinea pig bronchoalveolar lavage (BAL) model

(Gonzalo, J.A. et al, Immunity, 1996, 4, 1.)

BALs were obtained from Guinea Pigs (± compound) 24 h after ovalbumin (OA) exposure to eotaxin administered via inhalation. The animals were euthanized by cervical dislocation and exsanguinated. The lungs were lavaged with 50 ml of DulBecco's PBS (5x10cc), which was aspirated after a gentle chest massage. The BAL fluid was spun down and the pellet was resuspended in 0.25% NaCl to lyse residual erythrocytes. After centrifugation, the pellet was resuspended again in 0.9% NaCl. After a total cell count, slides were prepared and stained. The cells were differentiated into eosinophils, neutrophils and monocytes by counting a minimum of 200 cells and expressing the results as a percentage of total cells.

Alternatively, OA sensitized Guinea Pigs (± compound) were exposed to OA via inhalation 24 h after OA exposure and lungs were obtained as described above and assessed for eosinophil infltration.

The following examples are illustrative but not limiting of the embodiments of the present invention.

Example 1

1-Phenoxy-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone

a) 1-Bromo-3-(S)-(N-^{t}butyloxycarbonylamino)-4-(4-nitrophenyl)-2-butanone

N-^{t}Butyloxycarbonyl-4-nitrophenylalanine (3.28g, 10.6 mmol) was dissolved in dry THF (20 mL) and the solution cooled to -25°C. N-Methylmorpholine (1.1g, 10.6 mmol) was added followed by isobutyl chloroformate (1.44g, 10.6 mmol) at a rate such that the temperature did not exceed -25°C. After 5 minutes dry ether (25 mL) was added while cooling the reaction to -70°C. The mixture was filtered under argon and the filtrate treated with an ethereal solution of diazomethane (40 mmol). The mixture was allowed to warm to room temperature over 1h and stirred for an additional 2 hours. Excess diazomethane was purged with nitrogen, the solution evaporated and the residue taken up in ethyl acetate (50 mL). The solution was washed with saturated aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and evaporated to a pale solid. The solid was taken up in dry THF (25 mL), the solution cooled to 0°C and treated with a solution HBr in AcOH (7 mL). The reaction mixture was stirred at room temperature for 1hr and was washed with ether and saturated aqueous sodium bicarbonate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give the title compound as a white solid (3.3g ,80%).

b) 1-Phenoxy-3-(S)-amino-4-(4-nitrophenyl)-2-butanone hydrochloride

To the solution of 1-Bromo-3-(S)-(N-^{t}butyloxycarbonylamino)-4-(4-nitrophenyl)-2-butanone (0.25g, 0.65mmol), phenol (0.061g, 0.65mmol) and potassium carbonate (0.09g, 0.65mmol) in 2ml DMF was added tetra-n-butyl-ammonium iodide (2mg) and the resulting mixture was stirred overnight at room temperature. The mixture was diluted with ether (30ml) and washed with water. The organic layer was dried (MgSO4), filtered and concentrated to afford a white solid (0.15g, 58%). The solid was treated with 4N HCl (1ml) in dioxane and stirred at room temperature for 30 min. The solution was evaporated in vacuo, and the resulting solid was washed with diethyl ether to furnish the title product (0.1g, 80%) as a white solid.

c) 1-Phenyoxy-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone

To a suspension of 1-phenyoxy-3-(S)-amino-4-(4-nitrophenyl)-2-butanone hydrochloride (50mg, 0.15mmol) in THF (12ml) was added naphthoyl chloride (0.03g, 0.15mmol) and NaOH (0.012g, 0.3mmol). The reaction mixture was stirred at room temperature for 20min. The solution was evaporated to dryness, the solid was washed with water, ether and hexane to furnish the title compound as a white solid (40mg, 60%). MS (ES+) m/e 455 $[M+Na]^+$.

Example 2

1-Mercaptophenyl-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone

a) 1-Mercaptophenyl-3-(S)-amino-4-(4-nitrophenyl)-2-butanone hydrochloride

To a solution of 1-Bromo-3-(S)-(N-^{t}butyloxycarbonylamino)-4-(4-nitrophenyl)-2-butanone (0.25g, 0.65mmol), thiophenol (0.064g, 0.65mmol) and 2,6-lutudine (0.07g, 0.65mmol) in 2ml DMF was added tetra-n-butyl-ammonium iodide (2mg) and the resulting mixture was stirred overnight at room temperature. The mixture was diluted with ether (30ml), washed with 0.1N NaOH, 0.1N HCl and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford a white solid (0.2g, 74%). The solid (0.2g, 0.48mmol) was treated with 0.5ml 4N HCl in dioxane and stirred at room temperature for 30 min. The solution was evaporated in vacuo, and the resulting solid was washed with diethyl ether to furnish the title product (0.15g, 89%) as a white solid.

b) 1-Mercaptophenyl-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone

To a suspension of 1-mercaptophenyl-3-(S)-amino-4-(4-nitrophenyl)-2-butanone hydrochloride (50mg, 0.14mmol) in 12ml of THF was added naphthoyl chloride (0.03g, 0.15mmol) and NaOH (0.011g, 0.28mmol). The reaction mixture was stirred at room temperature for 20min., the solution was evaporated to dryness, the solid was washed with water, ether and hexane to furnish the title compound as a white solid (47mg, 70%). MS (ES+) m/e 963 $[2M+Na]^+$.

Example 3

1-Sulfonylphenyl-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone

1-Mercaptophenyl-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone (60mg, 0.13mmol) was dissolved in THF and treated with peracetic acid (0.07ml, 0.29mmol). The reaction mixture was stirred at room temperature for 16hrs. The

solution was evaporated to dryness, the solid was washed with ether and hexane to furnish the title compound as a white solid (52mg, 82%). MS (ES+) m/e 525 $[M+Na]^+$ 1027 $[2M+Na]^+$.

Example 4

1-Phenylamino-3-(S)-(N-(1-naphthoyl)amino)-4-(4-chlorophenyl)-2-butanone

a) 1-Bromo-3-(S)-(N-^{t}butyloxycarbonylamino)-4-(4-chlorophenyl)-2-butanone

Prepared as a white solid in 75% yield from N-^{t}butyloxycarbonyl-4-chlorophenylalanine according to the procedure of Example 1(a).

b) 1-Phenylamino-3-(S)-amino-4-(4-chlorophenyl)-2-butanone hydrochloride

A DMF solution (3mL) of 1-bromo-3-(S)-(N-^{t}butyloxycarbonylamino)-4-(4-chlorophenyl)-2-butanone (0.3g, 0.8mmmol), aniline (80mg, 0.8mmol) and sodium hydrogen carbonate (68mg, 0.8mmol) was stirred for 16h. The reaction mixture was diluted with ether (20mL), washed with saturated aqueous sodium hydrogen carbonate, brine and dried ($MgSO_4$). Evaporation gave a yellow solid which was crystallized from ether (220mg, 70%). The solid (150mg, 0.4mmmol) was treated with 0.7ml 4N HCl in dioxane and stirred at room temperature for 30 min. The solution was evaporated in vacuo, and the resulting solid was washed with diethyl ether to furnish the title product (0.1g, 76%) as a white solid. MS (ES+) m/e 289 $[M+H]^+$.

c) 1-Phenylamino-3-(S)-(N-(1-naphthoyl)amino)-4-(4-chlorophenyl)-2-butanone

Prepared as a white solid in 77% yield from 1-phenylamino-3-(S)-amino-4-(4-chlorophenyl)-2-butanone hydrochloride according to the procedure of Example 1(c). MS (ES+) m/e 443 $[M+H]^+$.

Example 5

(S)-2-(1-Naphthoylamino)-3-(4-nitrophenyl)-N-(N-phenyl-2-acetamido)propionamide

a). 2-Amino-N-phenylacetamide hydrochloride

N-BOC-Gly-OH (500mg, 2.9mmol) was dissolved in THF (10mL) and the solution cooled to -25°C before the addition of N-methylmorpholine (0.58g, 5.8mmol) and isobutylchloroformate (0.43g, 3.1mmol). After stirring for 10 min, aniline (0.29g, 2.9mmol) was added and the reaction mixture was warmed to room

temperature over 1 hr. Solids were removed, the filtrate was evaporated to dryness and the residue was dissolved in ethyl acetate (20mL). The solution was washed with water, dried ($MgSO_4$) and evaporated to yield a white solid (0.5g, 70%). MS (ES+) m/e 251 $[M+H]^+$, 273 $[M+Na]^+$, 523 $[2M+Na]^+$. The solid (0.35g, 1.4mmol) was dissolved in 2mL 4N HCl in dioxane and stirred at room temperature for 30 min. The solution was evaporated in vacuo, and the resulting solid was washed with diethyl ether to furnish the title compound (0.23g, 88%) as a white solid.

b). (S)-2-Amino-3-(4-nitrophenyl)-N-(N-phenyl-2-acetamido)propionamide hydrochloride

N-BOC-4-nitro-L-phenylalanine (0.346g, 1.1mmol) was dissolved in DMF (2 mL), 2-amino-N-phenylacetamide hydrochloride (0.23g, 1.2mmol) was added, followed by N-methylmorpholine (0.35g, 3.2mmol), HOBt (0.166g, 1.2mmol), and EDCI (0.235g, 1.2mmol). The mixture was allowed to stir at room temperature for 7 days. Water was poured into the flask, causing the crude product to precipitate. The solid was filtered and washed with Et_2O to furnish the product (0.48 g, 97% yield) as a white solid. The solid (0.48g, 1.1mmol) was dissolved in 4mL 4N HCl in dioxane and stirred at room temperature for 60 min. The solution was evaporated in vacuo, and the resulting solid was washed with diethyl ether to furnish the title product (0.4g, 97%) as a white solid. MS (ES+) m/e 343 $[M+H]^+$.

c). (S)-2-(1-naphthoylamino)-3-(4-nitrophenyl)-N-(N-phenyl-2-acetamido)propionamide

(S)-2-Amino-3-(4-nitrophenyl)-N-(N-phenyl-2-acetamido)propionamide hydrochloride (0.2g, 0.53mmol) was dissolved in DMF (2 mL), 1-naphthoic acid (0.1g, 0.58mmol) was added, followed by N-methylmorpholine (0.16g, 1.59mmol), HOBt (0.078g, 0.58mmol), and EDCI (0.11g, 0.58mmol). The mixture was allowed to stir at room temperature for 12h. Water was poured into the flask, causing the crude product to precipitate. The solid was filtered and washed with Et_2O to furnish the title compound (0.2 g, 76% yield) as a grey solid. MS (ES+) m/e 519 $[M+Na]^+$, 1015 $[2M+Na]^+$.

Example 6

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-chlorophenyl)propionylamino]-(*N*-phenyl)propionamide

a) 2-Amino-*N*-phenylpropionamide hydrochloride

Using the procedure of Example 1(a) above, N-BOC-L-Ala-OH was converted into the title compound in 81% yield. MS (ES+) m/e 165 $[M+H]^+$, 206.

b). (S),(S)-2-[2-amino-3-(4-chlorophenyl)propionylamino]-(*N*-phenyl)propionamide hydrochloride

Using the procedure of Example 1(b) above, 2-amino-*N*-phenylpropionamide hydrochloride was converted into the title compound in 82% yield.

c). (S),(S)-2-[2-(1-naphthoylamino)-3-(4-chlorophenyl)propionylamino]-(*N*-phenyl)propionamide

Using the procedure of Example 1(c) above, (S),(S)-2-[2-amino-3-(4-chlorophenyl)propionylamino]-(*N*-phenyl)propionamide hydrochloride was converted into the title compound in 82% yield in 51% yield.

MS (ES+) m/e 522 $[M+Na]^+$, 563 $[M+H+CH_3CN]^+$, 1015 $[2M+Na]^+$

Example 7

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)propionylamino]-(*N*-methyl-*N*-phenyl)propionamide

a). 2-Amino-*N*-methyl-*N*-phenylpropionamide hydrochloride

Using the procedure of Example 1(a) above, N-BOC-L-Ala-OH was converted into the title compound in 76% yield.

b). (S),(S)-2-[2-amino-3-(4-nitrophenyl)propionylamino]-(*N*-methyl-*N*-phenyl)propionamide hydrochloride

Using the procedure of Example 1(b) above, 2-amino-*N*-methyl-*N*-phenylpropionamide hydrochloride was converted into the title compound in 50% yield.

c). (S),(S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)propionylamino]-(*N*-methyl-*N*-phenyl)propionamide

Using the procedure of Example 1(c) above, (S),(S)-2-[2-amino-3-(4-nitrophenyl)propionylamino]-(*N*-methyl-*N*-phenyl)propionamide hydrochloride was converted into the title compound in 17%yield.

MS (ES+) m/e 525 $[M+H]^+$, 547 $[M+Na]^+$, 1071 $[2M+Na]^+$.

Example 8

(S),(S)-2-(1-Naphthoylamino)-3-(4-nitrophenyl)-N-(N-phenyl-2-phenylacetamido)propionamide

a). (S)-2-Amino-2-phenyl-N-phenylacetamide hydrochloride

Using the procedure of Example 1(a) above, N-BOC-(S)-phenylglycine was converted into the title compound in 63% yield.

b). (S),(S)-2-Amino-3-(4-nitrophenyl)-N-(N-phenyl-2-phenylacetamido)propionamide hydrochloride

Using the procedure of Example 1(b) above, (S)-2-amino-2-phenyl-N-phenylacetamide hydrochloride was converted into the title compound.

c). (S),(S)-2-(1-Naphthoylamino)-3-(4-nitrophenyl)-N-(N-phenyl-2-phenylacetamido)propionamide

Using the procedure of Example 1(c) above, (S),(S)-2-amino-3-(4-nitrophenyl)-N-(N-phenyl-2-phenylacetamido)propionamide hydrochloride was converted into the title compound in 74% yield.

MS (ES+) m/e 595 $[M+Na]^+$, 636 $[M+H+CH_3CN]^+$

Example 9

(S),(S)-2-[2-(1-Naphthoylamino)-3-(4-chlorophenyl)propionylamino]-*N*-(3-pyridyl)propionamide

a) (S)-2-Amino-*N*-(3-pyridyl)propionamide dihydrochloride

Using the procedure of Example 1(a) above, N-BOC-L-Ala-OH was converted into the title compound in 68% yield. MS (ES+) m/e 166 $[M+H]^+$, 207 $[M+H+CH_3CN]^+$.

b) (S),(S)-2-[2-Amino-3-(4-chlorophenyl)propionylamino]-*N*-(3-pyridyl)propionamide dihydrochloride

Using the procedure of Example 1(b) above, (S)-2-amino-*N*-(3-pyridyl)propionamide dihydrochloride was converted into the title compound in 67% yield. MS (ES+) m/e 347 $[M+H]^+$.

c) (S),(S)-2-[2-(1-Naphthoylamino)-3-(4-chlorophenyl)propionylamino]-*N*-(3-pyridyl)propionamide

Using the procedure of Example 1(c) above, (S),(S)-2-[2-amino-3-(4-chlorophenyl)propionylamino]-*N*-(3-pyridyl)propionamide dihydrochloride was converted into the title compound in 37% yield.
MS (ES+) m/e 501 $[M+H]^+$.

Example 10

(S),(S)-2-[2-(1-Naphthoylamino)-3-(4-chlorophenyl)-*N*-methylpropionylamino]-(*N*-phenyl)propionamide

a) (S)-2-*N*-Methylamino-*N*-phenylpropionamide hydrochloride

Using the procedure of Example 1(a) above, N-Me-N-BOC-L-Ala-OH was converted into the title compound in 75% yield. MS (ES+) m/e 179 $[M+H]^+$, 220 $[M+CH_3CN]^+$.

b) (S),(S)-2-[2-Amino-3-(4-chlorophenyl)propionylamino]-*N*-(phenyl)propionamide dihydrochloride

Using the procedure of Example 1(b) above, 2-amino-*N*-(phenyl)propionamide dihydrochloride was converted into the title compound in 58% yield. MS (ES+) m/e 360 $[M+H]^+$.

c) (S),(S)-2-[2-(1-Naphthoylamino)-3-(4-chlorophenyl)propionylamino]-*N*-(phenyl)propionamide

Using the procedure of Example 1(c) above, (S),(S)-2-[2-amino-3-(4-chlorophenyl)propionylamino]-*N*-(phenyl)propionamide dihydrochloride was converted into the title compound in 27% yield.
MS (ES+) m/e 536 $[M+Na]^+$, 577 $[M+Na+CH_3CN]^+$.

Example 11

(S),(S)-2-[2-(1-Naphthoylamino)-3-(4-nitrophenyl)-*N*-methylpropionylamino]-(*N*-phenyl)propionamide

a) (S),(S)-2-[2-Amino-3-(4-chlorophenyl)propionylamino]-*N*-(phenyl)propionamide dihydrochloride

Using the procedure of Example 1(b) above, the product from Example 6(a) was converted into the title compound in 29% yield. MS (ES+) m/e 371 $[M+H]^+$.

b) (S),(S)-2-[2-(1-Naphthoylamino)-3-(4-chlorophenyl)propionylamino]-*N*-(phenyl)propionamide

Using the procedure of Example 1(c) above, (S),(S)-2-[2-amino-3-(4-chlorophenyl)propionylamino]-*N*-(phenyl)propionamide dihydrochloride was converted into the title compound in 20% yield.

MS (ES+) m/e 547 $[M+Na]^+$, 588 $[M+Na+CH_3CN]^+$.

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Example 12

Inhalant Formulation

A compound of Formula (I) or (II), (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

Example 13

Tablet Formulation

Tablets/Ingredients		Per Tablet
1.	Active ingredient (Cpd of Form. I or II)	40 mg
2.	Corn Starch	20 mg
3.	Alginic acid	20 mg
4.	Sodium Alginate	20 mg
5.	Mg stearate	1.3 mg

Procedure for tablet formulation:

Ingredients 1, 2, 3 and 4 are blended in a suitable mixer/blender. Sufficient water is added portion-wise to the blend with careful mixing after each addition until the mass is of a consistency to permit its conversion to wet granules. The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen. The wet granules are then dried in an oven at 140°F (60°C) until dry. The dry granules are lubricated with ingredient No. 5, and the lubricated granules are compressed on a suitable tablet press.

Example 14

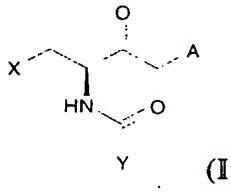
Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of Formula (I) or (II) in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then rendered sterile by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

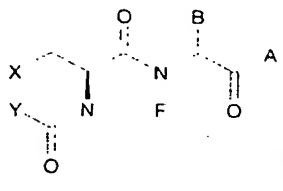
All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

What is claimed is:

1. A compound according to formula (I)or (II):



(I)



(II)

wherein:

A represents OR_1, NR_1 or SO_nR_1;

n = 0,1 or 2;

R_1 and R_2 are, independently, selected from the group consisting of hydrogen, C_{1-6}alkyl, alkylaryl, arylalkyl and aryl;

X represents optionally substituted aryl or heteroaryl;

Y represents optionally substituted aryl or heteroaryl;

C' represents NR_1R_2;

B represents hydrogen, methyl, aryl, alkylaryl or arylalkyl; and

F represents hydrogen, C_{1-6}alkyl or aryl.

2. A compound according to claim 1 wherein A is selected from the group consisting of O-phenyl, NH-phenyl, S-phenyl and SO_2-phenyl.

3. A compound according to claim 1 wherein C' is selected from the group consisting of NH-phenyl, $N(CH_3)$-phenyl and NH-(3-pyridinyl).

4. A compound according to claim 3 wherein F is selected from hydrogen or CH_3.

5. A compound according to claim1 selected from the group consisting of :

1-Phenoxy-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone;

1-Mercaptophenyl-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone;

1-Sulfonylphenyl-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone; and

1-Phenylamino-3-(S)-(N-(1-naphthoyl)amino)-4-(4-chlorophenyl)-2-butanone.

6. A compound according to claim 1 wherein the compound is selected from the group consisting of:

(S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)propionylamino]-(*N*-phenyl)acetamide;

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-chlorophenyl)propionylamino]-(*N*-phenyl)propionamide;

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)propionylamino]-(*N*-methyl-*N*-phenyl)propionamide;

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-chlorophenyl)propionylamino]-*N*-(3-pyridyl)propionamide;

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-chlorophenyl)-*N*-methylpropionylamino]-(*N*-phenyl)propionamide; and

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)-*N*-methylpropionylamino]-(*N*-phenyl)propionamide.

7. A compound according to claim 6 which is (S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)propionylamino]-(*N*-phenyl)acetamide.

8. A method of antagonizing a CCR-3 receptor by administering a compound according to claim 1.

9. A method according to claim 8 wherein the compound is selected from the group consisting of:

1-Phenoxy-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone;

1-Mercaptophenyl-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone;

1-Sulfonylphenyl-3-(S)-(N-(1-naphthoyl)amino)-4-(4-nitrophenyl)-2-butanone; and

1-Phenylamino-3-(S)-(N-(1-naphthoyl)amino)-4-(4-chlorophenyl)-2-butanone.

10. A method according to claim 8 wherein the compound is selected from the group consisting of:

(S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)propionylamino]-(*N*-phenyl)acetamide;

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-chlorophenyl)propionylamino]-(*N*-phenyl)propionamide;

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)propionylamino]-(*N*-methyl-*N*-phenyl)propionamide;

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-chlorophenyl)propionylamino]-*N*-(3-pyridyl)propionamide;

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-chlorophenyl)-*N*-methylpropionylamino]-(*N*-phenyl)propionamide; and

(S),(S)-2-[2-(1-naphthoylamino)-3-(4-nitrophenyl)-*N*-methylpropionylamino]-(*N*-phenyl)propionamide.

11. A method of treating an allergic disease comprising administering to a patient in need of treatment a safe and effective amount of a compound according to claim 1.

12. A method according to claim 11 wherein the disease is selected from the group consisting of bronchial asthma, eczema, conjunctivitis, allergic rhinitis, nasal polyposis, atopic dermatitis, pruritis and inflammatory bowel disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/05911

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/352, 616, 617, 619; 546/309; 564/152, 153, 161, 166

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,514,391 A (GORDON et al) 30 April 1985, column 23, example d.	1-12
Y	US 4,636,522 A (GORDON) 13 January 1987, column 15, example c.	1-12
Y	GUNDEL, W. H. Investigations on Quaternary Pyridinium Salts, XVIII).- Note on Synthetic Cyclopeptides with 1,4-Dihydronicotinamide Moiety. Liebigs Ann. Chem. 1985, pages 1280-1283, especially page 1281.	1-12
Y	SO et al. Lipase catalyzed synthesis of Peptides containing D-amino acid. Enzyme and Microbial Technology. 1998, Vol. 23, pages 211-215, especially page 214.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 24 MAY 2000	Date of mailing of the international search report 12 JUN 2000
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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

A61K 31/16, 31/44, 31/165; C07C 233/05; C07D 213/02

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/352, 616, 617, 619; 546/309; 564/152, 153, 161, 166